Serial No.

10/582,534

Page No.

2

Complete listing of all claims, with markings and status identifiers (currently amended claims showing deletions by strikethrough and additions by underlining)

1. (Canceled)

2. (Currently amended) A compound according to claim 1 of formula (I), $(R^2R^3) - A^7 - A^8 - A^9 - A^{10} - A^{11} - A^{12} - A^{13} - A^{14} - A^{15} - A^{16} - A^{17} - A^{18} - A^{19} - A^{20} - A^{21} - A^{22} - A^{23} - A^{24} - A^{25} - A^{26} - A^{27} - A^{28} - A^{29} - A^{30} - A^{31} - A^{32} - A^{33} - A^{35} - A^{36} - A^{37} - A^{38} - A^{39} - R^1$

<u>(I)</u>

wherein

A⁷ is L-His, Ura, Paa, Pta, Amp, Tma-His, des-amino-His, or deleted;

A⁸ is Ala, β-Ala, Gly, Ser, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A⁹ is Glu, N-Me-Glu, N-Me-Asp or Asp;

 A^{10} is Gly, Acc, β -Ala or Aib;

A¹¹ is Thr;

A¹² is Phe, Acc, Aic, Aib, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Cha, Trp or (X⁶, X⁷, X⁸, X⁹, X¹⁰)Phe;

A¹³ is Thr;

A¹⁴ is Ser or Aib;

A¹⁵ is Asp;

A¹⁶ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A¹⁷ is Ser;

A¹⁸ is Ser or Lys;

A¹⁹ is Tyr, Cha, Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Acc or (X⁶,X⁷,X⁸,X⁹,X¹⁰)Phe;

A²⁰ is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or (X⁶,X⁷,X⁸,X⁹,X¹⁰)Phe;

A²¹ is Glu;

 A^{22} is Gly, Acc, β -Ala, Glu or Aib;

A²³ is Gln or Glu;

A²⁴ is Ala, Aib, Val, Abu, Tle or Acc;

 A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

 $\underline{A^{26}}$ is Lys, Arg, hArg, Orn, Lys(N^{ϵ}-decanoyl)), HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A²⁷ is Glu, Leu, Aib or Lys;

Serial No.

10/582,534

Page No.

3

 A^{28} is Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, $(X^6, X^7, X^8, X^9, X^{10})$ Phe, Aic, Acc, Aib, Cha or Trp; A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A³⁰ is Ala, Aib or Acc;

A³¹ is Trp, Phe, 1Nal or 2Nal;

A³² is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, (X⁶,X⁷,X⁸,X⁹,X¹⁰)Phe or Ala;

A³³ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or (X⁶, X⁷, X⁸, X⁹, X¹⁰)Phe;

 A^{34} is Lys, Arg, hArg, Orn, HN-CH((CH₂)₂-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A³⁵ is β-Ala, D-Ala, Gaba, Ava, HN-(CH₂)_m-C(O), Aib, Acc, D-Arg or a D-amino acid;

 A^{36} is L- or D-Arg, D- or L-Lys, or Lys(N^{ϵ}-decanoyl) or Lys(N^{ϵ}-dodecanoyl) or D- or L-hArg, D- or L-Orn or HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), or HN-CH((CH₂)_{ϵ}-X³)-C(O);

 A^{37} is Gly, β -Ala, Gaba, Aib, Acc, Act, Apc, Aun, Ava, Pro, Dhp, Dmt, Pip, L- or

D- Arg, L- or D- Asp or Glu, Lys(N^{ϵ} -decanoyl), Lys(N^{ϵ} -dodecanoyl), Lys(N^{ϵ} -octanoyl), Lys(N^{ϵ} -octanoyl), or Ser(O-decanoyl);

A³⁸ is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Ado, Aib, Apc, Act, Arg, Ava, Gly, β Ala, Gaba, or HN-(CH₂)_s-C(O);

A³⁹ is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Ado, Aib, Apc, Act, Arg, Aun, Gly, β Ala, Gaba, Lys(N^e-octanoyl), HN-(CH₂)_s-C(O), or deleted;

R¹ is OH, NH₂; (C₁-C₃₀)alkoxy, or NH-X²-CH₂-Z⁰, wherein X² is a (C₀-C₂), (C₄-C₉) or (C₁₁-C₁₉)hydrocarbon moiety and Z⁰ is H, OH, CO₂H or CONH₂;

$$X^{4}$$
 N $-(CH_{2})_{f}$ -CH₃ -NH-C(O)-CH₂ N $-(CH_{2})_{2}$ -NH-C(O)-R¹³

or -C(O)-NHR¹², wherein X⁴ is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH₂-, and wherein f is, independently for each occurrence, an integer from 1 to 29 inclusive;

each of R^2 and R^3 is independently selected from the group consisting of H, (C_1-C_{30}) alkyl, (C_2-C_{30}) alkenyl, optionally substituted phenyl (C_1-C_{30}) alkyl, optionally substituted naphthyl (C_1-C_{30}) alkyl, hydroxy (C_1-C_{30}) alkyl, hydroxy (C_2-C_{30}) alkenyl, hydroxyphenyl (C_1-C_{30}) alkyl, and hydroxynaphthyl (C_1-C_{30}) alkyl;

wherein the phenyl group of said optionally substituted phenyl(C_1 - C_{30})alkyl moiety, and said naphthyl group of said optionally substituted naphthyl(C_1 - C_{30})alkyl moiety each is, independently for each occurrence, substituted with 1 or more substituents selected, independently for each occurrence, from the group consisting of halo, OH, NH₂, NO₂ and CN;

Serial	No.	

10/582,534

Page No.

or one of R^2 and R^3 is $(CH_3)_2$ -N-C=N(CH₃)₂, $(C_1$ - C_{30})acyl, $(C_1$ - C_{30})alkylsulfonyl, $C(O)X^5$,

; wherein Y is H, OH or

NH₂; r is 0 to 4; q is 0 to 4; and X^5 is (C_1-C_{30}) alkyl, (C_2-C_{30}) alkenyl, phenyl (C_1-C_{30}) alkyl, naphthyl (C_1-C_{30}) alkyl, hydroxy (C_1-C_{30}) alkyl, hydroxy (C_2-C_{30}) alkyl, hydroxyphenyl (C_1-C_{30}) alkyl or hydroxynaphthyl (C_1-C_{30}) alkyl;

 $X^6, X^7, X^8, X^9, X^{10}$ for each occurrence is independently selected from the group consisting of H, (C_1-C_6) alkyl, OH, OR⁴, NO₂, CN, and halo;

 R^4 is (C_1-C_{30}) alkyl, (C_2-C_{30}) alkenyl, phenyl (C_1-C_{30}) alkyl, naphthyl (C_1-C_{30}) alkyl, hydroxy (C_1-C_{30}) alkyl, hydroxy (C_2-C_{30}) alkenyl, hydroxyphenyl (C_1-C_{30}) alkyl or hydroxynaphthyl (C_1-C_{30}) alkyl; e is, independently for each occurrence, an integer from 1 to 4 inclusive;

m is, independently for each occurrence, an integer from 5 to 24 inclusive;

s is, independently for each occurrence, an integer from 5 to 10 or from 12 to 20 inclusive;

n is, independently for each occurrence, an integer from 1 to 5, inclusive;

each of R¹⁰ and R¹¹ is, independently for each occurrence, H, (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl, (C₁-

C₃₀)alkylsulfonyl, –C((NH)(NH₂)) or

: and

 R^{12} and R^{13} each is, independently for each occurrence, (C_1-C_{30}) alkyl; provided that:

when A⁷ is Ura, Paa or Pta, then R² and R³ are deleted;

when R^{10} is (C_1-C_{30}) acyl, (C_1-C_{30}) alkylsulfonyl, $-C((NH)(NH_2))$ or

, then R^{11} is H or (C_1-C_{30}) alkyl;

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-38 or -39)NH₂ or hGLP-1(7-38 or -39)OH;

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-38 or -39)NH₂ or hGLP-1(7-38, or -39)OH wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not $(Arg^{26,34}, Lys^{38})hGLP-1(7-38)-E$, $(Lys^{26}(N^{\epsilon}-alkanoyl))hGLP-1(7-38)-E$, $(Lys^{26,34}-bis(N^{\epsilon}-alkanoyl))hGLP-1(7-38)-E$

10/582,534

Page No.

5

alkanoyl))hGLP-1(7-38)-E, (Arg²⁶, Lys³⁴(N^e-alkanoyl))hGLP-1(8-38)-E, (Arg^{26,34}, Lys³⁶(N^e-alkanoyl))hGLP-1(7-38)-E, wherein E is -OH or -NH₂;

(iv) a compound of formula (I) is not Z^1 -hGLP-1(7-38)-OH, Z^1 -hGLP-1(7-38)-NH₂; wherein Z^1 is selected from the group consisting of:

- (a) (Arg²⁶), (Arg³⁴), (Arg^{26,34}), (Lys³⁶), (Arg²⁶, Lys³⁶), (Arg³⁴, Lys³⁶), (D-Lys³⁶), (Arg³⁶), (Arg^{26,34}, Lys³⁶) or (Arg^{26,36}, Lys³⁴);
- (b) (Asp^{21}) ;
- (c) at least one of (Aib⁸), (D-Ala⁸) and (Asp⁹); and
- (d) (Tyr⁷), (N-acyl-His⁷), (N-alkyl-His⁷), (N-acyl-D-His⁷) or (N-alkyl-D-His⁷); and
 (v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups
 (a) to (d);

or a pharmaceutically acceptable salt thereof.

- 3. (Original) A compound according to claim 2, wherein A^9 is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc, 1Nal, 2Nal, or Aic; A^{16} is Val, Acc or Aib; A^{19} is Tyr, 1Nal or 2Nal; A^{20} is Leu, Acc or Cha; A^{24} is Ala, Aib or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O); A^{28} is Phe, 1Nal or 2Nal; A^{29} is Ile or Acc; A^{30} is Ala or Aib; A^{32} is Leu, Acc or Cha; and A^{33} is Val, Lys or Acc; or a pharmaceutically acceptable salt thereof.
- 4. (Currently amended) A compound according to elaim 1 claim 2, wherein A^8 is Ala, Gly, Ser, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, 1Nal, 2Nal, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, β -Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, β -Ala, Ado, A6c, A5c, D-Arg or Acc; A^{37} is Gly, Aib, β -Ala, D-Ala, Pro, Asp, Aun or D-Asp; A^{38} is D- or L- His, Asn, Ser, Apc, Act, Gly, β -Ala or Gaba; and A^{39} is Ser, Thr or Aib; or a pharmaceutically acceptable salt thereof.
- 5. (Original) A compound according to claim 4 or a pharmaceutically acceptable salt thereof, X^4 for each occurrence is -C(O)-; and R^1 is OH or NH₂; or a pharmaceutically acceptable salt thereof.

Page No.

6. (Original) A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R^2 is H and R^3 is (C_1-C_{30}) alkyl, (C_2-C_{30}) alkenyl, (C_1-C_{30}) alkylsulfonyl,

7. (Original) A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R^{10} is (C_1-C_{30}) acyl, (C_1-C_{30}) alkylsulfonyl or

-C(O)-CH
$$_2$$
—N—(CH $_2$) $_f$ -CH $_3$, and R 11 is H $_2$

8. (Original) A compound according to claim 7 or a pharmaceutically acceptable salt thereof, wherein R^{10} is (C_4-C_{20}) acyl, (C_4-C_{20}) alkylsulfonyl or

9. (Currently amended) A compound according to elaim 1 claim 2, wherein: A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, 1Nal, 2Nal, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, β -Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, β -Ala, Ado, A6c, A5c or D-Arg; and A^{37} is Gly, Aib, β -Ala, D-Ala, Pro or D-Asp; A^{38} is D- or L- His, Asn, Ser, Gly, β -Ala or Gaba; and A^{39} is Ser, or deleted; X^4 for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R^1 is OH or NH₂; R^{10} is

-C(O)-CH₂-N N-(CH₂)_f-CH₃ , and
$$R^{11}$$
 is H;

or a pharmaceutically acceptable salt thereof.

Page No.

10. (Original) A compound according to claim 9, wherein R¹⁰ is (C₄-C₂₀)acyl, (C₄-

$$-C(O)-CH_2-N$$
 $N-(CH_2)_f-CH_3$

C₂₀)alkylsulfonyl or

, or a pharmaceutically

acceptable salt thereof.

11. (Currently amended) A compound according to elaim 1 claim 2 wherein said compound is according to the formula:

(Aib^{8,35}, Arg^{26,34}, Phe³¹, Pro³⁷, Ser^{38,39})hGLP-1(7-39)-NH₂; (SEQ ID NO:1)

(Aib^{8,35,37}, Arg^{26,34}, Phe³¹, Asn³⁸)hGLP-1(7-38)-NH₂; (SEQ ID NO:2)

(Aib^{8,35,37}, Arg ^{26,34}, Phe³¹, Ser ³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:3)

(Aib^{8,35,37}, Gaba³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:4)

(Aib^{8,35,37}, Arg^{26,34}, Phe³¹, His³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:5)

(Aib 8,35 , Arg 26,34 , Phe 31 , β -Ala 37 , His 38)hGLP-1(7-38) NH₂; (SEQ ID NO:6)

(Aib^{8,35,37}, Arg^{26,34}, D-His³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:7)

(Aib^{8,35,37}, β-Ala³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:8)

(Aib^{8,35}, Arg^{26,34}, β -Ala³⁷, His³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:9)

(Aib^{8,35,37}, Arg^{26,34}, Phe³¹, Gly³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:10)

(Aib^{8,35,37}, Arg^{26,34}, Gly³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:11)

 $(Aib^{8,35,37}, Arg^{26,34}, \beta - Ala^{38}) hGLP - 1 (7-38) \ NH_2; \ (SEQ \ ID \ NO:12)$

(Aib^{8,35,37}, Arg^{26,34}, Gaba³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:13)

 $(Aib^{8,35,37}, Arg^{34}, Phe^{31}, His^{38})hGLP-1(7-38) NH_2; (SEQ ID NO:14)$

(Aib^{8,35,37}, Arg^{26,34}, His³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:15)

(Aib^{8,35,37}, Arg^{26,34}, Phe³¹, Gaba³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:16)

(Aib^{8,35,37}, Arg^{26,34}, Phe³¹, Ava³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:17)

(Aib^{8,35,37}, Arg^{26,34}, Ava³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:18)

(Aib^{8,35,37}, Arg³⁴, Phe³¹, D-His³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:19)

 $({\rm Aib^{8,35,37},\,Arg^{34},\,Phe^{31},\,Gly^{38}})hGLP\text{-}1(7\text{-}38)\;NH_2;\,(SEQ\;ID\;NO\text{:}20)$

(Aib^{8,35,37}, Gly³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:21)

(Aib^{8,35,37}, Arg^{26,34}, Phe³¹, D-His³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:22)

(Aib^{8,35}, Arg^{26,34}, Phe³¹, β -Ala³⁷, D-His³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:23)

(Aib $^{8,35,37},\,Arg^{26,34},\,Phe^{31},\,\beta-Ala^{38})hGLP-1(7-38)\;NH_2;$ (SEQ ID NO:24)

(Aib^{8,35}, Arg^{26,34}, Phe³¹, β -Ala ^{37,38})hGLP-1(7-38) NH₂; (SEQ ID NO:25)

Serial No.

10/582,534

Page No. :

8

(Aib^{8,35,37}, Arg³⁴, Phe³¹, β -Ala³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:26) or (Aib^{8,35,37}, Arg³⁴, Phe³¹, Gaba³⁸)hGLP-1(7-38) NH₂; (SEQ ID NO:27) or a pharmaceutically acceptable salt thereof.

- 12. (Currently amended) A pharmaceutical composition comprising an effective amount of a compound according to elaim 1 claim 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.
- 13. (Withdrawn-currently amended) A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to elaim 1 claim 2 or a pharmaceutically acceptable salt thereof.
- 14. (Withdrawn-currently amended) A method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis, neurodegenerative disease, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, hypertension, treatment of respiratory distress, disorders wherein the reduction of food intake is desired, hypoglycemia and malabsorption syndrome associated with gastroectomy or small bowel resection, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to elaim 1 claim 2 or a pharmaceutically acceptable salt thereof.
- 15. (Withdrawn) A method according to claim 14 wherein said disease is Type I diabetes or Type II diabetes.

16-27. (Canceled)